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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SPITMANN, Knut, H.
P.O. Box 10101
S-220 10 Lund
SUÈDE

Date of mailing (day/month/year)
09 November 2000 (09.11.00)

Applicant's or agent's file reference
GA 282 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/SE00/00614

International filing date (day/month/year)
30 March 2000 (30.03.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
ASKETORP, Göran
Gambro Lundia AB
P.O. Box 10101
S-220 10 Lund
Sweden

State of Nationality:
State of Residence:
Telephone No.: +46/46-16-91-69
Facsimile No.: +46/46-16-91-89
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
SPITMANN, Knut, H.
P.O. Box 10101
S-220 10 Lund
Sweden

State of Nationality:
State of Residence:
Telephone No.: +46/46-16-91-79
Facsimile No.: +46/46-16-91-89
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
F. Baechler

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003648092

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 09 November 2000 (09.11.00)	
International application No. PCT/SE00/00614	**Applicant's or agent's file reference** GA 282 PCT
International filing date (day/month/year) 30 March 2000 (30.03.00)	**Priority date** (day/month/year) 30 March 1999 (30.03.99)
Applicant EDGSON, Raymond, Anthony et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 October 2000 (18.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

F. Baechler

Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00614

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 2/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0428009 A1 (GAMBRO AB), 22 May 1991 (22.05.91), figures 1-4, claims 1-17 --	1-20,21-40
X	WO 9613279 A1 (ABBOTT LABORATORIES), 9 May 1996 (09.05.96), figures 1-2, claims 1-8 -- --------	1-20,21-40

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000	20 -07- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Agneta Änggård/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 00/00614

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0428009 A1	22/05/91	DE 69013119 D,T	26/01/95
		DK 428009 T	14/11/94
		ES 2060894 T	01/12/94
		JP 3268762 A	29/11/91
		SE 500294 C	30/05/94
		SE 8903855 A	17/05/91
WO 9613279 A1	09/05/96	AU 3965795 A	23/05/96

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Spitmann Knut H
P O Box 10101
220 10 Lund

ANKOM
2001 -07- 26

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	25-07-2001
Applicant's or agent's file reference: GA 282 PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/00614	30-03-2000	30-03-1999

Applicant
Gambro Lundia AB
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in som Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary axamination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Hediye Güzel Telephone No. 08-782 25 00

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

ANKOM
2001 -07- 2 6

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference GA 282 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE00/00614	International filing date *(day/month/year)* 30.03.2000	Priority date *(day/month/year)* 30.03.1999
International Patent Classification (IPC) or national classification and IPC7 A61L 2/04		
Applicant Gambro Lundia AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.10.2000	20.07.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Leif Törn /BS Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00614

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIM[redacted]Y EXAMINATION REPORT

International application No.
PCT/[redacted]00/00614

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-40	YES
	Claims		NO
Inventive step (IS)	Claims	1-40	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-40	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents were cited in the International Search Report:

(1) WO 9613279
(2) EP 0 428 009

(1) relates to a method and system for sterilizing heat sensitive drugs which prevents degradation of the drug from heat. The method includes providing separate relatively less heat sensitive component solutions of the drug for independent heat sterilization and then transferring the sterilized component solutions to a holding tank where they are mixed to form a final solution. Thus, instead of sterilizing the heat sensitive final product, the non-heat sensitive components are sterilized separately prior to mixing.

(2) relates to a method for the preparation of a sterile diaslysis fluid. Water is heated to, and kept at, sterilizing temperature whereby added concentrates are sterilized in the water.

None of the documents discloses a method wherein a heat sensitive fluid is sterilized by heat from a non-heat sensitive fluid through mixing, where the mixing results in a lowering of the temperature of the non-heat sensitive fluid. Therefore, the subject matter of claims 1-40 is considered to fulfil the requirements of novelty and inventive step. The industrial applicability is obvious.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61L 2/04

A1

(11) International Publication Number: WO 00/57928

(43) International Publication Date: 5 October 2000 (05.10.00)

(21) International Application Number: PCT/SE00/00614

(22) International Filing Date: 30 March 2000 (30.03.00)

(30) Priority Data:

9901165-2	30 March 1999 (30.03.99)	SE
9903331-8	16 September 1999 (16.09.99)	SE

(71) Applicant *(for all designated States except US)*: GAMBRO LUNDIA AB [SE/SE]; P.O. Box 10101, S-220 10 Lund (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: EDGSON, Raymond, Anthony [GB/GB]; Ramscroft, Malting Lane, Litlington, Nr. Royton (GB). DUNKLEY, Michael, John [GB/GB]; 20 Manhattan Drive, Cambridge CB4 1JL (GB). HAMMOND, Richard, J. [GB/GB]; 16 Granta Terrace, Great Shelford, Cambridge CB4 3NF (GB). WILKINSON, Eric [GB/GB]; 14 Chequers Croft, Hilton, Cambridgeshire PE18 9PD (GB).

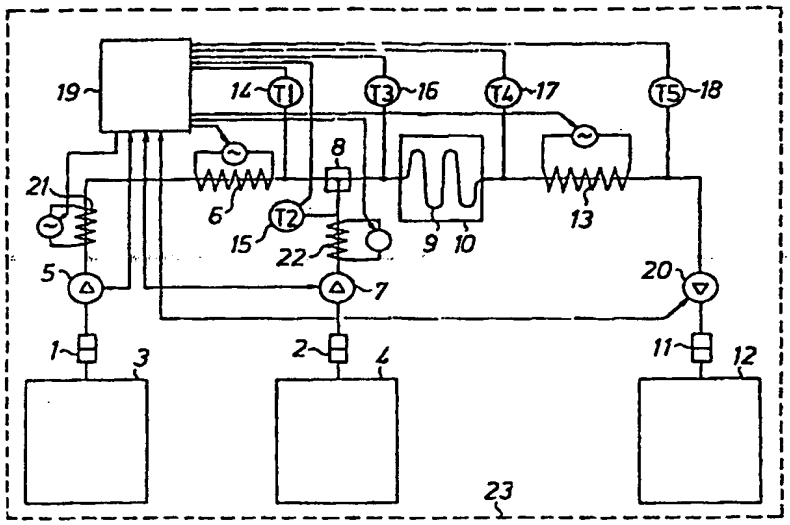
(74) Agent: ASKETORP, Göran; Gambro Lundia AB, P.O. Box 10101, S-220 10 Lund (SE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: METHOD AND APPARATUS FOR STERILISING A HEAT SENSITIVE FLUID



(57) Abstract

Method and apparatus for sterilising a heat sensitive fluid, such as a fluid for peritoneal dialysis. The fluid is provided as a first heat sensitive component and a second less heat sensitive component. The less heat sensitive component is heated to a temperature higher than a sterilising temperature. The two components are then mixed to thereby heat the first component and cool the second component. The heating of the first component is controlled to obtain a mixing temperature equal to the desired sterilising temperature. The mixed components are maintained at the sterilising temperature during a sterilisation time so that a sterilisation dose is obtained, whereafter the mixed components are cooled and delivered to a recipient. Preferably, the method is performed on line with continuous flows of fluids whereby the heated second fluid flow component heats the first, possibly preheated, component to sterilising temperature.

FOR THE PURPOSES OF INFORMATION ONLY

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TITLE

Method and apparatus for sterilising a heat sensitive fluid

FIELD OF INVENTION

The present invention relates to a method and device for producing a sterile medical solution. More specifically, the invention relates to a method and device for producing a sterile medical solution comprising a heat sensitive component, such as glucose.

Medical solutions intended for mammals, specifically for use in humans, are required to be sterile before being infused or applied to the mammal.

One available method for sterilising a solution is to heat the solution to a sterilising temperature and to hold the solution at the sterilising temperature during a sterilising time. To obtain a sterile medical solution intended for infusion, the solution is normally heated in an autoclave to 121°C for 20 minutes to thereby produce said sterile medical solution. After the sterilising time has elapsed, the solution should be cooled to a physiologically acceptable temperature before infusion.

Known methods and apparatus for sterilising a solution are disclosed in for example GB 1450030, GB 1504334, GB 2034584 and US 5603894. These prior art publications describe the preparation of a medical solution starting from tap water and producing pure water via a reverse osmosis device, mixing a concentrate with the pure water to produce a non-sterile medical solution, passing the non-sterile medical solution through an on-line autoclave and delivering the sterile medical solution to a recipient, such as a storage bag or a patient.

In the prior art, the complete medical solution is first prepared in a non-sterile condition and then passes through an

autoclave. If the medical solution comprises heat sensitive components, these must not be exposed to too high a temperature. Normally, the temperature is increased up to the sterilising temperature and the medical solution is maintained at the sterilising temperature for a sterilising time. If the temperature is 121°C, which is normal in an autoclave, the sterilising time is 20 minutes to obtain a sterilising dose F_0 of 20 minutes, see below for further details. Since the sterilising effect is approximately exponential, an increase of the temperature by 10°C means a lowering of the sterilising time by ten times. If a sterilising temperature of 131°C is used, the sterilising time should be 2 minutes, and if a sterilising temperature of 141°C is used, the sterilising time should be 12 seconds, in order to obtain a sterilising effect F_0 of 20 minutes.

If the medical solution comprises a heat sensitive component, like glucose, that component will deteriorate during the heat treatment. An example of a medical solution containing a heat sensitive component is dialysis fluid for peritoneal dialysis (PD). The decomposition or heat deterioration starts at a much lower temperature than the sterilising temperature and is present also at room temperature. In order to safeguard the heat sensitive material, very short heating and cooling periods are desired so that the time/temperature profile becomes more or less rectangular. This is of greater importance if high sterilising temperatures and short sterilisation times are used.

It is known to produce sterile medical solutions by including the medical solution in a bag and placing the bag inclusive of the medical solution in an autoclave for heating and sterilisation.

A variant of this method is described in WO 93/09820, in which the medical solution is divided in two portions, one comprising glucose at high concentration and the other comprising the rest of the solution. The double bag is heat sterilised in an autoclave. Shortly before use, the contents of the two chambers are mixed to produce the sterile medical solution. In this way, the heat sensitive component, glucose, can be auto-

claved under more appropriate conditions such as at a low pH of approximately pH=3.2 and at a high concentration of approximately 50%, i.e. 500 g glucose per litre glucose solution.

A variant of the same methods is described in WO 97/05852 disclosing a three-chamber-bag, in which two of the chambers comprise glucose solution and the third chamber comprise the rest of the solution. The glucose chambers may also include ionic components like calcium, magnesium and sodium.

A further variant is described in PCT patent application PCT/SE98/02146.

In the afore mentioned concepts, the glucose portion is sterilised separately from the remaining portion of the solution. However, in order to fully sterilise the large compartment, the small glucose compartment may be over sterilised resulting in deterioration of the heat sensitive component. A remedy for that problem is described in Swedish patent application SE 9803627-0, filed at the Swedish Patent Office October 23, 1998.

The problem of deterioration of a substance during autoclaving is also recognised in other fields of use, such as the production of sterile milk products. In order to obtain a fast heating and cooling of the product, it is not sufficient to use heat transfer via a heat transferring surface, like a heat exchanger. Instead, the product is mixed with steam at a predetermined temperature and pressure to condense the steam in the milk product. The milk product is sterilised by retention in a holding zone for a certain time period and at a temperature of 120 - 150°C, and is then transferred to a flash cooling step, in which water is evaporated in an evaporation chamber to rapidly cool the product. Such a process is described in, for example, WO 98/07328.

DISCLOSURE OF INVENTION

A first object of the present invention is to provide a method and device for producing a sterile medical solution having a gentle treatment of the heat sensitive component.

Another object of the present invention is to provide a method and device in which inexpensive heaters and heat exchangers can be used.

A third object of the present invention is to provide a method and device for sterilising a medical solution in which the time/temperature profile for heating the heat sensitive component is essentially rectangular.

Thus, there is provided, according to the invention, a method of sterilising a heat sensitive fluid, comprising

providing the fluid as a first heat sensitive component and a second less heat sensitive component;

heating the second component to a first temperature higher than a predetermined sterilising temperature;

mixing the first component with the second component to thereby heat the first component and cool the second component, whereby the mixed components obtain a mixing temperature, which is at least equal to said sterilising temperature;

maintaining said mixed components at substantially said sterilising temperature during a sterilisation time so that a predetermined sterilisation dose is obtained; and

delivering said mixed component to a recipient.

Preferably, the first temperature is controlled to obtain a mixing temperature, which is at least equal to said sterilising temperature. Moreover, it is preferred to cool the mixed components before delivery to said recipient.

The first heat sensitive component may comprise glucose or a glucose polymer and the second less heat sensitive component may comprise water. More specifically the second component may include electrolytes, selected from the group of substances comprising: sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium bicarbonate and sodium lactate.

It may be advantageous to preheat the first component. Normally, the temperature is above the boiling temperature at normal atmospheric pressure and, thus, the first and second components are maintained at a high pressure sufficient to prevent boiling.

In an embodiment, the first and second components are provided as flows of fluid, whereby the flow rate of the second component may be larger than the flow rate of the first component.

In order to separate the flow rate determination from the pressurising means, the flow rates are determined with a pair of scales or a flow meter and the pressure is provided by a separate pump.

In one embodiment of the invention, the complex fluid is divided in several fluid components, which are sterilised separately, as described above, and sequentially and then mixed to the complex fluid. This may be performed by providing sources of concentrated fluid components and pure water; pumping a first concentrated fluid from said sources of concentrated fluids, to increase the pressure thereof; pumping pure water to increase the pressure thereof and heating said pure water to said first temperature; mixing said first concentrate and heated pure water and maintaining the mixed fluids at a sterilising temperature for a sterilising time to effect sterilisation; delivering said sterilised and diluted concentrate fluid to a recipient; repeating the above method steps for each of the concentrated fluid components, to provide the final complex fluid in the recipient. The concentrated fluid may be preheated before being mixed with the heated water, for example by a heat exchanger by heat recovery from the sterilised fluid, which is cooled thereby.

The second fluid may be preheated by heat recovery in a heat exchanger from the sterilised fluid, which is thereby cooled, and further heated to said first temperature by a separate heating device, such as an electric heater. The heating device may be controlled by a temperature sensor positioned downstream of the maintaining step, to ensure that sterilising temperature is obtained.

BRIEF DESCRIPTION OF THE DRAWINGS

Further objects, advantages and features of the invention will appear from the following detailed description of several embodiments shown on the drawings.

Fig. 1 is a schematic view of a first embodiment of a device for sterilising a heat sensitive fluid according to the invention.

Fig. 2 is a schematic view similar to Fig. 1 of a second embodiment of a device according to the invention.

Fig. 3 is a schematic view similar to Fig. 2 of a portion of a third embodiment of a device according to the invention.

Fig. 4 is a cross-sectional view of a heat sterilisable connector used in the device according to Fig. 2.

Fig. 5 is a schematic view similar to Fig. 1 of a third embodiment of the device according to the invention.

Fig. 6 is a schematic view of a first embodiment of a cycler which may be connected to the device according to Fig. 2 or 4.

Fig. 7 is a time diagram of the fluid flows in the cycler according to Fig. 6.

Fig. 8 is a schematic view similar to Fig. 6 of a second embodiment of the cycler.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The fluid to be sterilised comprises a first non-heat-sensitive portion and a second heat sensitive portion. According to the invention, the two portions are delivered separately to the sterilising device into two separate inlets 1 and 2.

With reference to Fig. 1, the first non-heat-sensitive component, which may comprise sodium chloride dissolved in water, is enclosed in a vessel 3 connected to the inlet 1. The second heat sensitive component, which may comprise glucose, is enclosed in a vessel 4 connected to the inlet 2. The fluid components are preferably provided at a temperature at which each component is relatively stable, such as room temperature.

The first fluid portion from vessel 3 provided to inlet 1 is impelled by a first pump 5 to a heater 6, in which the first fluid portion is heated to a first high temperature. The second fluid portion is impelled by a second pump 7 and mixed with the first fluid portion in a mixing point 8 arranged downstream of the heater 6. During the mixing, the second fluid portion is rapidly heated to a sterilising temperature, while the first

fluid portion is cooled to the same sterilising temperature. The second fluid portion does not make direct contact with the heater surface and so damage is minimised.

In order to promote rapid mixing, the fluids are impelled at such conditions that turbulent flow prevails at least after the mixing point 8. In addition, flow mixing means may be arranged in the flow path, such as at the mixing point 8 or in the flow path downstream of mixing point 8. Such flow mixing means may be flanges or wings in the flow path.

The mixed fluid portions pass through a sterilising tube section 9 dimensioned to provide a predetermined resident or sterilising time for the mixed fluids at the sterilising temperature. The tube section may be insulated as indicated by box 10 to maintain the mixed fluids at the sterilising temperature for the sterilising time. After the sterilising time, the mixed fluids are sterile, since the second fluid portion has been subjected to the sterilising temperature during a sterilising time and the first fluid portion has been exposed to a still higher temperature and still longer time, thus being oversterilised.

The sterilising dose is a function of temperature and time and is defined according to the formula:

$$F_0 = \int_0^t 10^{(T-121)/10}\, dt$$

in which

F_0 = the sterilisation dose in minutes
T = temperature
t = time

If the sterilising temperature is 121°C and the time is 20 minutes, a sterilisation dose of 20 minutes is obtained. If the sterilising temperature is 141°C and the time is 12 seconds, a sterilisation dose F_0 of 20 minutes is also obtained. A sterilising dose F_0 of 20 minutes is considered sufficient, however,

in certain applications, a sterilising dose F_0 of 10 minutes or even lower may be sufficient.

In the above example, the first fluid portion may comprise sodium chloride at a concentration of 150 mM, sodium lactate at a concentration of 38,8 mM, magnesium chloride at a concentration of 0,56 mM and calcium chloride at a concentration of 1,89 mM. The second fluid portion may comprise glucose at a concentration of 40%, i.e. 400 g glucose per litre solution. The first fluid portion flow rate is 45 ml/min and the second fluid portion flow rate is 5 ml/min. The resulting mixture has the following composition: sodium chloride 135 mM, sodium lactate 35 mM, magnesium chloride 0,5 mM, calcium chloride 1,7 mM and glucose 4%. The first fluid portion is heated from 20°C to 155°C by the heater 6. The second fluid portion is heated from 20°C to 141°C during mixing, while the first fluid portion is cooled from 155°C to 141°C. The resident or sterilising time is 12 seconds resulting in a sterilising dose F_0 of 20 minutes. The resulting sterilised fluid mixture is cooled by a cooler 13 and delivered to an outlet 11 and collected in a vessel 12. A pump 20 or other device may be arranged to control the flow to the vessel 12. The sterile fluid may be used as a peritoneal dialysis solution to be delivered to the peritoneal cavity of a patient.

Other medical fluids may be produced by the device according to the invention, such as hemodialysis solutions, infusion solutions used in hemodiafiltration or hemofiltration, replacement fluids for infusion in the blood, wound irrigation solutions, rinsing solutions etc. Moreover, nutrition solutions often comprises amino acids, which are heat sensitive, and glucose, which is heat sensitive, and cannot be sterilised together with amino acids. Certain drugs, such as insulin, may be produced or included in a fluid administered to a patient, and the drug component may be heat sensitive. Certain medical fluids comprise peptides, proteins or fragments thereof, which normally are heat sensitive. Preservation fluids for blood component handling may also comprise heat sensitive components, at least glucose. In certain cases, glucose is replaced with or complemented with glucose polymers, di-sacharides, tri-

sacharides etc. Certain carboxylic acids are heat sensitive and may be included in such fluids. Solutions comprising calcium or magnesium ions and carbonate or bicarbonate ions may precipitate at exposure to a sterilising temperature, and need to be sterilised with the carbonate or bicarbonate separate from the calcium or magnesium containing solution.

In order to control the above procedure, one or several temperature sensors are provided. A first temperature sensor 14 may be arranged immediately downstream of the heater 6 to determine the temperature of the first fluid portion after heating. A second temperature sensor 15 may be arranged between the second inlet 2 and the mixing point 8 to determine the temperature of the second fluid before mixing. A third temperature sensor 16 may be arranged downstream of the mixing point to determine the mixing temperature. A fourth temperature sensor may be arranged downstream of the sterilising section 9 to determine the sterilising temperature. A fifth temperature sensor 18 may be arranged downstream of cooler 13 to determine the temperature of the fluid delivered to vessel 12. Not all of these five temperature sensors are needed so one or several thereof may be excluded.

A control processor 19 may be arranged to control the sterilising device according to the invention. As shown in Fig. 1, the five temperature sensors are connected to the processor as well as the pumps 5, 7 and 20 to provide measurements of the temperatures and flow rates. The pumps 5, 7 and 20 may be volumetric pumps also acting as flow meters. Alternatively, separate flow meters may be provided. The processor controls the heater 6 to provide the required temperature downstream of the heater, as measured by temperature sensor 14, to provide the sterilising temperature after mixing as measured by temperature sensors 16 and 17. The processor calculates the residence time in the sterilising section 9 based on the flow rates of pumps 5 and 7 and the known volume of the sterilising section 9. Finally, the processor may determine the obtained sterilising dose F_0.

The control processor 19 may obtain all necessary information in order to calculate the sterilising effect from the flow rates of pumps 5 and 7 and the temperature of sensor 17.

As also shown in Fig. 1, the fluids provided to inlets 1 and 2 may be preheated by preheaters 21 and/or 22.

Since the sterilising apparatus shown in Fig. 1 is intended to heat the fluids to temperatures well above 100°C, it is required to keep the fluids from boiling. This may be done by enclosing the entire apparatus in an enclosure 23, as shown by broken lines in Fig. 1, and raising the pressure inside the enclosure to a pressure sufficient to prevent boiling, such as 3 - 6 Bar absolute pressure.

It is known that glucose decomposes when exposed to heat, and is thus a heat sensitive component of the fluid. Glucose also decomposes during storage. It is known that several factors influence the decomposition of glucose, among which are pH, temperature, time, glucose concentration and mixing with certain ionic components. Glucose decomposes into components, some of which may be more or less toxic or are able to induce toxic reactions by including precursors for such reactions. If the resulting fluid is to be used as a medical fluid for infusion into a human being or other mammal, the toxic components or precursors should be minimised.

In order to sterilise the fluid it is necessary to expose the fluid to sterilising conditions. There are several methods available, such as heat sterilisation (autoclaving), filter sterilisation and other methods. The present invention is limited to heat sterilisation.

During heat sterilisation, it is known that decomposition of glucose can be minimised if glucose is sterilised during a short time at a high temperature. The rationale is that the decomposition reaction is less sensitive to high temperature than the sterilising reaction.

In order to minimise the decomposition before sterilisation, it is advantageous to store the fluid at a low pH and at a high concentration, which is suggested according to the invention. The pH may be from 2,6 - 5,0 and preferably pH=3,2. The concentration may be above 15% or above 20% with 40% - 50%

being preferred, calculated as weight of glucose per litre solution.

The sterilisation may take place during a short time and at a pH of below about 5,5 and at a final dilution concentration. It is believed that the short time is of greater importance than the other factors for avoiding decomposition into toxic components of glucose during the sterilisation process.

It is also recognised that glucose may decompose into precursors for AGE, advanced glucosylation end products. When a glucose solution comprising precursors for AGE contacts proteins in the body, a non-enzymatic reaction takes place resulting in AGE formation. The long term effect of AGE is still not well known. Gentle heat sterilisation of glucose as suggested in the present invention is expected to reduce the level of glucose degradation products of the type of AGE precursors.

An alternative embodiment of the invention is shown in Fig. 2. In this embodiment the sterilising device according to the invention is integrated in a PD monitor arranged to provide a PD solution to a patient. The PD solution is prepared from two concentrates provided in two concentrate bags 51 and 52 and connected to concentrate input connectors 56 and 57, and a supply of pure water, for example provided from a reverse osmosis RO-unit 53 connected to a water input connector 58 for connection to a potable water supply. The sterilised PD fluid is delivered to a PD cycler 55, which is, in turn, connected to a PD fluid output connector 59 for delivery to the patient.

Each of the three input connectors and the output connector is arranged as a heat sterilisable connector device as shown in more details in Fig. 4. Such a heat sterilisable connector device 30 is described in WO 96/05883 and comprises a spike 31 opening into a bore 32 in a housing 33. The bore is arranged to receive a connector 35 connected to a vessel or bag, for example comprising the concentrate. The connector has a shape which is complementary to the bore, such as cylindrical, and may be inserted into the bore to seal the bore by means of an O-ring 37. The connector is further provided with a membrane 35a being pierceable by said spike 31. The connector 35 is operable by a piston 39 to be pushed into the bore into a

first position sealing the bore 32. The piston is operable by a motor 38 operating a screw and nut arrangement 38a or any other suitable driving device like a pneumatically or hydraulically operated device.

During operation, the connector 35 is inserted in the bore 32 into co-operation with the O-ring 37. A rinsing, disinfecting and/or sterilising fluid is circulated through the spike 31 into the bore 32 and out through a side opening 36 in the bore. The spike, bore and the membrane of the connector are thus rinsed, disinfected and/or sterilised. When the rinsing, disinfecting and/or sterilising operation is finished, the piston 39 pushes the connector 35 further into the bore 32 so that the spike 31 penetrates the membrane 35a to thereby establish a connection between the spike and the vessel connected to the connector 35. At the same time, the connector seals off the side opening 36 and an area around the spike 31.

The connector device 30 may also be used without inserting a connector 35 by passing the piston 39 into the bore 32 into co-operation with the O-ring seal 37 to establish a flow path via spike 31 into side opening 36.

Returning now to Fig. 2, each of the inputs 56, 57 and 58 and the output 59 is arranged as a connector device 30 of Fig. 4. Input 56 is arranged to connect a first concentrate bag 51 to a first metering pump 60 and input 57 is arranged to connect a second concentrate bag 52 to a second metering pump 61. Input 58 is connected to RO-unit 53 and a third pump 62 is arranged to pump pure water from RO-unit 53.

Pumps 62 and 60 are driven to mix the concentrate from bag 51 with pure water from RO-unit 53 to provide a desired concentration. A conductivity cell 63 may be arranged to measure the conductivity of the mixture and may control the pump 60 and/or 62 to obtain the required conductivity and thus the desired concentration. Pump 62 is preferably driven to provide a constant flow of for example 54 ml/min and at the same time increase the pressure to 3 - 6 Bar absolute pressure to avoid boiling during sterilisation. The fluid provided so far is the first heat-insensitive fluid mentioned above.

The first fluid passes through a first heat exchanger 64 comprising a primary circuit 64a for heating the first fluid, for example from 20°C to 100°C. Then, the first fluid passes through a heater 65 such as an electric heater powered by an electric power supply 66 to heat the first fluid to a temperature of 155°C.

The second, heat sensitive, fluid from bag 52 is pumped by pump 61, at a flow rate of 6 ml/min to a mixing point 67 immediately downstream of heater 65 to mix with the first fluid. The second fluid is thus rapidly heated from room temperature to a temperature of 141°C by being mixed with the hot first fluid, which at the same time cools down to 141°C.

Then, the mixed fluids pass through a sterilising unit 68 comprising a tube 68a of a length suitable for providing a residence time giving the required sterilising time, such as 12 seconds. The tube is embedded in an insulating material 68b to minimise the temperature decrease during the residence time.

Immediately downstream of the sterilising unit 68 is a temperature sensor 69, which controls the power supply 66 so that the temperature is the desired sterilising temperature, such as 141°C.

Pump 61 is controlled to deliver the heat sensitive fluid in the amount desired. For example, if the heat sensitive fluid is glucose at a concentration of 40%, the flow rate should be 6 ml/min to give a final concentration of 4% if the first flow rate is 54 ml/min. If a concentration of 1,5% is desired, the flow rate should be 2,1 ml/min and if a concentration of 2,5% should be obtained, the flow rate should be 3,6 ml/min. In each case, the temperature sensor adjusts the power supply to heat the first fluid to a suitable temperature so that the sterilising temperature is obtained.

After the sterilising unit 68, the now sterilised fluid enters the secondary circuit 64b of the heat exchanger 64 to rapidly decrease the temperature of the sterilised fluid, for example to 60°C. Then, the sterilised fluid passes a flow restrictor 70 to decrease the pressure to close to atmospheric pressure. Preferably, the flow restrictor 70 is controlled by a pressure sensor 71, so that the pressure before the restrictor

is the desired pressure to prevent boiling, such as 6 Bar absolute pressure.

From the flow restrictor 70, the sterilised fluid is delivered to the output 59, which is connected to a PD cycler 55. A pressure relief valve 72 is arranged to connect the sterilised fluid to a waste 73 if the pressure of the fluid exceeds a predetermined value, such as 150 mmHg above atmospheric pressure.

The PD cycler may be of the type described in WO 95/20985, comprising a pressure chamber. A disposable line set is connected between the outlet connector and the patient and comprises a heater bag and a drain bag, a drain line and a supply line. The heater bag and a drain bag are arranged on a weighing device, such as a pair of scales. Four valves in a valve unit are arranged to operate on the drain and supply lines. Finally, the line set comprises a PD connector for connection to a catheter into the peritoneal cavity of the patient. The PD fluid from outlet 59 is supplied to the heater bag via the valve unit until the scales indicate that the heater bag has been filled to a predetermined volume, such as 3 litres. Then the patient is drained by exposing the pressure chamber to a subpressure to withdraw fluid in the peritoneal cavity of the patient out via the open valve unit into the drain bag. The combined weight of heater bag and drain bag is weighed and the drain phase is terminated when it is determined that the drain flow rate is below a predetermined limit or a drain time has elapsed. The drain flow rate is determined by means of the weighing device. Then, the pressure chamber is exposed to an overpressure and the valve unit is opened to allow the fresh sterilised PD fluid to flow into the peritoneal cavity of the patient. The flow rate and the delivered fluid volume is monitored and the fill phase is terminated when a desired fill volume has been delivered. The temperature of the heater bag is controlled by a heating device and temperature sensor so that the fluid delivered has a temperature of about 37°C. Finally, the drain bag is emptied to the waste by opening the valve unit and exposing the pressure chamber to an overpressure.

When the patient has been exposed to a fluid exchange as described above, the PD fluid is left in the peritoneal cavity for a dwell time until the next exchange cycle. During the dwell, the sterilising device provides new sterile fluid to the heater bag. It takes about 33 minutes to produce a fill volume of 2 litres if sterile fluid is produced at 60 ml/min.

It may be desirable to include a cooler 82 after the flow restrictor 70 to further decrease the temperature before delivering the fluid to the heater bag. The cooler may be a Peltier cooler or a heat exchanger of conventional design, using cold water or a cooling medium as heat energy absorption medium. A cooler 91, such as a Peltier cooler, may alternatively or additionally be placed after residence device 68 and before heat exchanger 64, in order to rapidly cool the heat sensitive mixture to a safe temperature, such as from 141°C to 120°C. In this way, the heat sensitive component is heated rapidly from room temperature to sterilisation temperature of 141°C at mixing point 67, is maintained at the sterilising temperature during 12 seconds by residence device 68 and is then rapidly cooled to 120°C by Peltier cooler 91 and then further cooled to room temperature in the slightly slower heat exchanger 64

The sterilising device needs to be disinfected at suitable intervals, for example once per day or once per week. For that purpose, the side openings of the connector devices 56, 57, 58 and 59 are used. The side opening 83 of RO inlet 58 is connected to the side opening 82 of outlet 59 via a line 84. The side opening 85 of first inlet 56 is connected to the flow line 86 between RO inlet 58 and the pump 62 via a line 87. The side opening 88 of second inlet 57 is connected to the line 89 between heater 65 and sterilising unit 68 via a line 90.

During disinfection, the sterilising device is filled with pure water obtained from the RO-unit. Then, connectors 57, 58 and 59 are disconnected from the respective sources and the piston is arranged in the position in conjunction with the O-ring, in order to seal the bore 32 of the connector opening, see Fig. 4.

Thus, the RO-inlet connector 58 and the outlet connector 59 are connected via line 84 and side openings 82 and 83. The

second inlet connector 57 is in the same position so that a circulating path is obtained via pump 61, line segment 89, line 90, side opening 88 and inlet 57. A disinfecting solution is provided in a vessel connected to the first inlet 56. The disinfecting fluid may be sodium carbonate, citric acid or any other known disinfection fluid. Pumps 62 and 61 are operated to circulate the water in the circuits. Finally, pump 60 is operated to infuse disinfection fluid into the water until a sufficient disinfectant concentration has been obtained. The surplus water is rejected via relief valve 72 to the waste 73. Pump 62 circulates the disinfection fluid through the complete sterilisation device and the outlet 59 is connected to the inlet 58 via line 84 to complete the circuit. The disinfection fluid may be left in the machine until the next use. Before the next use, the machine is rinsed with pure water via inlet 58 from the source of RO-water.

Descaling with citric acid or other descaling agent is performed in the same manner.

In order to avoid dripping from the connectors, the inlet connectors 56, 57 and 58 and the outlet connector 59 are positioned at the highest position of the flow path and at the same level.

The machine may be emptied by opening all inlets 56, 57 and 58 and the outlet 59 and by opening the relief valve 72, which is positioned at the lowest point of the flow path and allowing air to enter all lines and devices.

During chemical disinfection and/or descaling, the heater 65 may be turned off or adjusted to heat the fluid to a low temperature. The flow restrictor 70 may be opened.

In heat sterilisation, the fluid in the entire circuit is heated to 121°C and circulated for at least 20 minutes to obtain sterilisation of the entire circuit. In this case, pressure relief valve 72 is operated to permit a pressure of 2 Bar, thereby preventing boiling of the water in the circuit at 121°C.

The same or a similar procedure may be used for sterilising the flow path of the sterilising device. The fluid circuit is arranged for a treatment with all connectors inserted in

respective bore 32 in the non-engaged position. The circuit is full with water, which is circulated by pump 62. Flow restrictor 70 is opened and relief valve 72 is adjusted to a pressure of 2 - 3 Bar absolute pressure. First inlet connector 56 is operated to connect the vessel 51 to the circuit. Then, pump 60 is operated to introduce some fluid (electrolyte fluid) in the circuit until the pressure reaches about 2 - 3 Bar absolute pressure. Since the fluid circuit is relatively non-compliant, the volume of fluid introduced is very small. Then, the heater is activated to heat the water present in the circuit to a temperature of 121°C and the circulation continues for 20 minutes or longer, until sterilisation is obtained. Pump 61 is operated simultaneously to sterilise the circuit comprising inlet connector 57.

After sterilisation has been obtained, RO inlet 58 is activated to connect RO-unit 53 to the circuit and at the same time disconnect bypass line 84. Pump 60 is stopped, and heater 65 is activated. Flow restrictor 70 is activated and pressure relief valve 72 is adjusted to the normal value of 150 mmHg overpressure. Thus, sterile water is produced and delivered to the waste 73 via relief valve 72. Then, the second inlet is activated to connect vessel 52 and pumps 60 and 61 are operated to provide a PD fluid. When stable conditions are obtained, the outlet 59 is activated to deliver sterilised fluid to the heater bag.

During the drain and fill phases of the PD cycler, the sterilising device may continue to produce PD fluid. However, since the valve unit is closed, the PD fluid produced is directed to the waste 73 via relief valve 72. Since the drain and fill phases may last up to 20 minutes or more, a considerable amount of PD fluid is wasted. To minimise such waste, pumps 60 and 61 may be stopped during the periods when the heater bag is not being filled, and the sterilising device is only producing and wasting sterile water.

The first and/or second concentrates may comprise the same substances or components as mentioned above, however, with the contents of the first vessel 51 concentrated by omitting some

of the water. The contents of the first vessel may be concentrated for example 30 - 40 times.

In an alternative embodiment, the PD fluid is intended to comprise bicarbonate instead of or in addition to lactate. Calcium cannot be included in the same vessel as bicarbonate, because of the risk of precipitation of calcium carbonate. In that case, the calcium chloride may be included in the second vessel 52 in a suitable concentration. The calcium concentration will then be proportional to the glucose concentration, which may result in a calcium neutral PD fluid. Another advantage of including the calcium ions in the second vessel is that scaling of the pipe system is avoided before the mixing point 67, and the requirement for descaling would decrease.

Each of the sterilisable connectors may be replaced by a conventional connector device and a three way valve of conventional type, as shown in more detail in Fig. 3, which shows an alternative embodiment of the invention.

Fig. 3 shows an alternative design of a mixing system delivering the mixed fluids in parallel through the residence device. Fig. 3 shows only the right-hand portion of Fig. 2 to the right of pump 62 and pressure sensor 70. The left-hand portion may be identical to the embodiment of Fig. 2. The same components as in Fig. 2 have received the same reference numerals but adding 100 to the reference numbers. Thus, there is shown a heat exchanger 164 comprising a primary circuit 164a and a secondary circuit 164b and a pump device 164c. An electrolyte solution or pure water is conducted through line 189 through heat exchanger primary circuit 164a and a second heater 165, for example an electric heater controlled by a temperature sensor 169.

A first bag 152a comprising a heat sensitive first component such as glucose is connected via a connector 192a to a three-way valve 157a. The first component passes from the three-way valve 157a to a pump 161a and further to a mixing point 167a, in which the first component is heated to 141°C by mixture with a heated electrolyte component, having a temperature sufficient for promoting such heating by mixing, the temperature being for example 155°C. The mixing temperature is

controlled by a temperature sensor 169a, which operates a throttle valve 193a arranged before the mixing point 167a. By throttling the valve 193a, a sufficient flow rate for obtaining said temperature is adjusted.

A second bag 152b comprising a heat sensitive second component, such as amino acids, is connected via a connector 192b to a three-way valve 157b. The second component passes from the three-way valve 157b to a pump 161b and further to a mixing point 167b, in which the second component is heated to 141°C by mixture with a heated electrolyte component, having a temperature sufficient for promoting such heating by mixing, the temperature being for example 155°C. The mixing temperature is controlled by a temperature sensor 169b, which operates a throttle valve 193b arranged before the mixing point 167b. By throttling the valve 193b, a sufficient flow rate for obtaining said temperature is adjusted.

The two heat sensitive components heated to sterilising temperature by mixture with the electrolyte component are handled in parallel in two separate lines 194a and 194b, which pass in parallel through the residence device 168, the pre-cooler 191, if present, and to heat exchanger secondary circuit 164b. After cooling in the heat exchanger, the two fluids are mixed in a Y-connector 195 before entering the restriction device 70, see Fig. 2. The bags 152a and 152b are weighed and when a sufficient amount of fluid has been taken out from each bag, valve 157a and/or valve 157b are switched to stop the flow of first and/or second components from bags 152a, 152b, respectively.

During sterilisation, the three-way valves 157a and 157b are connected according to the broken lines in Fig. 3, in order to pass fluid, by means of pumps 161a and 161b in the fluid lines to and from the three-way valves 157a and 157b via lines 190a and 190b.

It is realised that more than two heat sensitive components may be handled in parallel by adding further bags 152 and further lines 194. Of course, the same procedure may be adopted for components which are less heat sensitive, to obtain a simple system, whereby the electrolyte component may be re-

placed with pure water, and thus, the electrolytes may be added one by one or several at a time.

A further alternative embodiment of the invention is shown in Fig. 5. From the left, the device 100 comprises a connector 101 for connection to a source of pure water, such as an RO-unit (not shown). The device further comprises three concentrate connectors 102, 103 and 104, which may be integrated into a single connector device. Each of connectors 102, 103 and 104 connects to a vessel or bag comprising a concentrate, such as a first bag 105 comprising a concentrated bicarbonate solution, a second bag 106 comprising electrolytes, such as sodium chloride, magnesium chloride, calcium chloride, and sodium lactate, at a predetermined pH, and a third bag 107 comprising glucose at a concentration of 50%. Of course, the bags include the components necessary for the final solution as discussed in more detail below. The components are divided into separate bags because they cannot be stored together or they cannot be sterilised together, or for other reasons.

Alternatively, one or more of the vessels or bags 105, 106, 107 may comprise a powder instead of a solution in which case appropriate dissolution means may be provided.

Conveniently, the bags 105, 106 and 107 are combined into a single assembly. The combined assembly of bags is attached to a weighing device 108, so that the weight of the assembly is monitored. The connectors 102, 103 and 104 are attached to the ends of flexible tubes of PVC or other suitable pliable material, so that the connectors and tubes do not significantly influence the weight of the assembly.

The RO inlet connector 101 is connected to a line system including a first inlet line 109. Inlet line 109 is provided with a inlet valve 110, to isolate the device 100 if required. Inlet valve 110 is normally closed, but is opened upon activation by a control device 111 shown by broken lines. The control device may be a computer or microprocessor or any other control device. Normally, it is the control computer of the complete device.

Inlet line 109 further comprises a heater 112 and a temperature sensor 113, which operate together to adjust the

temperature of incoming pure water to a predetermined temperature of e.g. 25°C, in order to make the device independent of incoming water temperature.

Inlet line 109 further comprises a flow meter 114 for measuring the complete inlet flow through inlet connector 101, for a purpose to be described later.

Downstream of flow meter 114, inlet line 109 is divided into water line 115 and concentrate line 116. Water line 115 comprises a first pump 117 for increasing the pressure of the water in water line 115 downstream of the pump to a pressure of 2 - 6 Bar absolute pressure. The pressure is measured by a first pressure sensor 118 and monitored by a second pressure sensor 119. The first pressure sensor 118 is connected to the control system of computer 111, while the second pressure sensor 119 is connected to a parallel supervising system for ensuring the safety of the system. Several of the sensors are duplicated in this manner to provide independent data to the supervisory system or processor, even if not explicitly indicated in the drawings.

Water line 115 further comprises a valve 120 and a primary circuit of a heat exchanger 121. In the heat exchanger, the water in water line 115 is heated from about 25°C to about 131°C in heat exchanger 121, at a flow of about 120 ml/min. The temperature of the heated water is monitored by temperature sensor 122. Finally, water line 115 comprises a second heater 123, for heating the water to a still higher temperature, such as about 145°C. The hot water is delivered to a mixing point 124.

In concentrate line 116, there is a valve 125 for connecting the normally closed concentrate line 116 to water line 115. Further downstream, concentrate line 116 comprises three concentrate valves 126, 127 and 128 and a reversible second pump 129. The second pump 129 is arranged to withdraw concentrate solutions or fluids from any one of concentrate bags 105, 106 or 107 depending on the positions of valves 126, 127 and 128. The second pump 129 further increases the pressure of the fluid in concentrate line 116 to a pressure of 2 - 6 Bar absolute pressure.

Downstream of second pump 129 is arranged a valve 130, and therefrom, the concentrate fluid is delivered to a second primary circuit of heat exchanger 121 in order to preheat the concentrate solution from e.g. room temperature to about 131°C. From heat exchanger 121, the concentrate solution is delivered to mixing point 124.

Upstream of the second pump 129 is arranged a temperature sensor 131 for measuring the temperature of the incoming concentrate fluid, and downstream of the second pump is arranged a pressure sensor 132 for measuring that sufficient pressure has been obtained. As indicated before, these sensors may be duplicated for supervisory purposes.

In mixing point 124, the two fluid lines 115 and 116 are joined so that the heated water in line 115 is mixed with preheated concentrate in line 116, and the mixture is transported in mixed fluid line 133. Mixed fluid line 133 comprises a residence device 134, normally being a length of tube of a length to produce a predetermined residence time at a predetermined rate of flow to effect sterilisation of the fluid in the residence device 134. The residence device 134 is preceded by a temperature sensor 135 and followed by a temperature sensor 136. These temperature sensors control the heater 123 to ensure that sterilising conditions are obtained in the residence device 134, such as a minimum temperature of 141°C for 12 seconds.

From the residence device 134, the sterilised and mixed fluid is passed to the secondary circuit of heat exchanger 121, at a temperature of approximately 141°C. The sterilised fluid is rapidly cooled to about 37°C.

Downstream of the heat exchanger, mixed fluid line 133 comprises sterilised fluid at a temperature suitable to be delivered to a patient or a storage bag. The temperature is monitored by a temperature sensor 137. Finally, a valve 138 directs, when activated, the fluid to an outlet connector 139, via a restrictor device 140, for lowering the pressure to atmospheric pressure.

The restrictor device may be a small hole in a piece of metal, the hole being dimensioned to reduce the pressure from 6

Bar to 1 Bar at the desired flow rate of, for example, 140 ml/min. An alternative design would be to use a controllable throttle valve, which is controlled by the processor in dependence of pressure sensor readings. A third alternative would be to use a throttle device or the pressure relief type, which adjust the differential pressure over the throttle device to a predetermined pressure drop of, for example, 5 Bar. A fourth alternative would be to use a throttle device controlled to deliver fluid at an output pressure of no more than a predetermined safe pressure of, for example, 1.25 Bar, in which case the pumps are operated to ensure that the pressure before the throttle device is sufficiently high, for example 6 Bar.

It is noted that the on-line autoclave as described is always operated at a predetermined minimal flow rate of not less than a predetermined flow rate, for example 120 ml/min, in order to ensure that the autoclave is maintained sterile. As soon as the flow rate drops below said predetermined minimum flow rate, the sterility conditions may be hampered or the autoclave may not be controlled to operate at proper temperatures. The autoclave may be designed to operate different flow rates above said minimum flow rate. In order to always maintain a minimal flow rate, any excess fluid produced is sacrificed to the waste.

If the mixed and sterilised fluid cannot be delivered out via the output connector 139, a valve 141 is activated to deliver the fluid to a sump or waste via a waste line 142. Waste line 142 further comprises a primary circuit of a second heat exchanger 143, a pressure sensor 144, a restrictor device 145 and a valve 146 until the fluid is delivered to the waste 147. A temperature sensor 148 arranged upstream of heat exchanger 143 and another temperature sensor 149 arranged downstream of valve 146 are used to measure the temperatures of the waste fluid.

The device according to Fig. 5 may be operated in different modes. One mode of operation will be described below, namely sequential delivery of the components of the final fluid. It is, however, understood that the device may operate as described in connection with Fig. 2 as well.

In the sequential operation mode, water is first delivered in inlet line 109 at a constant rate of 120 ml/min from inlet connector 101, via flow meter 114, in which the flow rate is monitored, and via water line 115 and via first pump 117 to raise the pressure so that the boiling temperature of the fluid is above the temperature anywhere in the circuit. If the maximum temperature is about 150°C, the pressure should be above 4.8 Bar or preferably about 6 Bar absolute pressure. The exact pressure is dependent on the adjustment and operation of restriction device 140. The water further passes the mixing point 124 and enters the mixed fluid line 133 and reaches valve 138, which directs the flow to waste line 142, via valve 141 and further to the sump. The outlet connector 139 is connected to a recipient, normally a bag, such as a heater bag described below.

When all conditions are checked and the device delivers sterilised water, valve 138 is switched to direct the sterilised water to the outlet connector 139 via restrictor 140.

Substantially at the same time, or shortly thereafter, valve 127 in concentrate line 116 is opened and concentrate pump 129 is activated, with valve 130 in an open condition, to pump concentrate fluid from electrolyte bag 106, via heat exchanger 121 to mixing point 124. The concentrate pump 130 is operated to provide a flow rate of approximately 20 ml/min. At the same time, the weight of the concentrate assembly is monitored by weighing device 108. If the intention is to provide 1 litre of final solution and the concentrate fluid in bag 106 has a concentration of 1:40, the flow is continued for about 1 minute and 15 seconds, until the weighing device indicate that a volume of 25 ml has left the bag 106, whereby 25 ml is the amount required from concentrate bag in 1 litre of final fluid (1:40).

Then, valve 127 is switched off and valve 125 is opened for a short time, such as 15 seconds, to rinse the concentrate line 116.

For including the second concentrate, which may be glucose, bag 107 is connected to the concentrate pump by closing valve 125 and opening valve 128. If the glucose concentrate

fluid has a concentration of 50%, the concentrate pump is driven 1 minute per percent concentration to be required in the final fluid at 20 ml/min. If 4% is required, which is the maximum contemplated for a PD fluid, the glucose concentrate is dosed in 4 minutes.

After this step, the concentrate line 116 is again rinsed with water, for example for 15 seconds.

Thereafter, the bicarbonate bag 105 is connected. The bicarbonate is normally stored at a concentration of about 1000 mmol/l. First, valve 125 is closed and valve 126 is opened so that concentrate pump 130 pumps bicarbonate fluid out of bag 105. The flow rate may be the same, 20 ml/min, and the mixing and sterilisation of bicarbonate fluid is discontinued when the weighing device determines that the required quantity has been removed from bag 105. If the final solution should contain 15 mmol/l, the concentrate pump is operated for 45 seconds to take 15 ml of concentrated bicarbonate solution out of bag 105.

Finally, the concentrate line is rinsed once again and water is delivered to the outlet connector, until the final volume of fluid has been delivered to the bag connected at the outlet connector, which is determined by flow meter 114 in combination with the weight losses measured by weighing device 108 and calculated into volumes by computer 111, taking into account the different densities of the concentrate fluids.

This final filling of water also means that the mix of fluid in the bag connected to the outlet connector is agitated and mixed thoroughly.

During the complete sterilisation process described above, valves 138 and 141 are maintained in the same position directing all fluid to the outlet connector 139. Thus, all fluid produced is delivered to the receiver, thereby minimising the time required for the preparation of the complete fluid.

In the example above, 1 litre of final solution has been prepared, but in PD it is more normal that 2 litres are generated each time, or any other volume as required by the user.

It is contemplated that the concentrate fluid bags may include concentrate fluid required for a final fluid volume of

12 - 25 litres or more if required. Then, the above sequence is repeated for each batch of 2 litres to prepare.

In certain applications for PD, bicarbonate is not used, but lactate is used as the sole buffer. In that case, the third bag in the concentrate assembly is unnecessary, and only two bags may be used. In that case, valve 126 is always closed.

To prepare one batch of 1 litre (1,5% glucose concentration), takes about 7 minutes and 45 seconds, supposing that the RO unit delivers pure water at 120 ml/min and 25 ml electrolytes, 15 ml bicarbonate and 30 ml glucose are used. Thus, the waiting time between each PD exchange of about 2 litres has to be more than 15,5 minutes. This might be limiting in some circumstances as appears from an explanation of the drain and fill phases of a PD treatment below.

In Fig. 6 is schematically shown a PD cycler 200 intended to be used in the present invention. The PD cycler comprises a pressure chamber 201 enclosing a heater bag 202 and a waste bag 203. The heater bag 202 is connected to the outlet connector 139 of fluid sterilisation device 100 of Fig. 5 for receiving a fresh sterilised fluid for introduction into heater bag 202. Heater bag 202 is connected with connector 139 via a first tube 204 ending with a connector 205 mating with connector 139 and comprising a valve 206. A second tube 207 connects heater bag 202 with a connector 208 to a patient (not shown) and the second tube 207 is controlled by a second valve 209. A third tube 210 connects the patient connector 208 to the drain bag 203 via a third valve 211. Finally, a fourth tube 212 connects drain bag 203 with a waste line 213 via a valve 214. Heater bag 202 and drain bag 203 rest on scales 215 which monitor the combined weight of the two bags.

The operation of the PD cycler as schematically disclosed in Fig. 6, appears from the diagram of Fig. 7. The diagram indicates the fluid volumes of the heater bag and drain bag during the different phases.

After priming, which is more closely described below, the first phase of the treatment is a drain phase, at the start of which the heater bag is full of fluid, normally about 2,4 litres, and the drain bag is empty. The patient is connected

and the third valve 211 is opened and a subpressure is exerted in pressure chamber 201. Fluid is withdrawn from the patient into drain bag 203 at a flow rate depending on the patient and the subpressure, normally from 150 - 300 ml/min. When the peritoneal cavity of the patient is almost empty, which may be indicated by a decrease of the drain flow as measured by the scales 215, the drain phase is terminated. The drain phase is normally 7 - 10 minutes.

The second phase is a fill phase, in which the peritoneal cavity of the patient is filled with fresh fluid contained in heater bag 202. An overpressure is exerted in pressure chamber 201 and valve 209 is opened, while the other valves are closed. The fill flow rate depends on the patient and the overpressure and may be 150 ml/min. The fill phase is normally 10 - 15 minutes.

The third phase is the empty drain bag phase, in which an overpressure is exerted in the pressure chamber 201 and valve 214 is open. The fluid in the drain bag is directed to a waste line 213. The volumes are always monitored by the scales 215. The third phase may be about 2 minutes, since a high overpressure may be used and the flow restriction is minimal.

The fourth phase is heater bag fill with valve 206 open. In this case, normally a subpressure is exerted in the pressure chamber 201. Fluid is received from the sterilising device 100 connected to connector 205 at a flow rate of about 120 ml/min. The fourth phase is normally 15 - 17 minutes.

Thus, a complete cycle is 34 - 44 minutes. During a night treatment of 8 hours, it is possible to exchange 22 - 28 litres, in batches of 2 litres.

If it is desired to increase the fluid volume further, the times in the different phases have to be shortened. It is noted that the heater bag fill time of 15 - 17 minutes could be shortened by increasing the flow rate of fluid from steriliser 100. However, increasing the flow rate means considerable cost increases.

Instead it is noted that the flow rate of the fluid delivered from steriliser 100 is monitored by the steriliser by flow meter 114 and weighing device 108. Thus, it is possible to fill

the heater bag during (part of) the drain cycle as indicated by the broken line 216 in Fig. 7. This is done by opening valve 211 during the heater bag fill phase, before the heater bag fill phase is terminated, such as 10 minutes in advance. If the drain phase is terminated before the heater bag is filled, the drain phase has to be continued until the heater bag filling is completed. However, it is no drawback to continue the drain phase longer, since that only results in some further fluid being drained, which normally is an advantage. Since the flow from the steriliser is known, the PD cycler still has full control of the flow by using the reading from the scales and subtracting the inflow from the steriliser. In this way, almost the complete drain phase can be saved in the cycle time, i.e. up to 10 minutes.

Another way of saving time is to fill the heater bag during the empty drain bag phase. It is recognised that the pressure chamber needs to have an overpressure to empty the drain bag. However, the sterilising device is able to deliver sterilised fluid under a slight overpressure. Thus, if valve 214 is open to pass fluid to the waste and valve 206 is open to allow fluid to enter the heater bag, and if there is an over-pressure inside the pressure chamber, the heater bag may be filled during the empty drain phase. Moreover, the pressure does not need to be reversed during the rest of the heater bag fill cycle, which normally is considerably longer than the empty drain bag phase. In this operation mode, it is still possible to keep accurate control over the ultrafiltration, since the volume of fluid drained from the patient and the volume of fluid filled into the patient are under full control of the mass balance device 215.

If the cycle time needs to be further shortened, that is possible by the addition of a storage bag in the line set as indicated in Fig. 8. It is noted that the steriliser has to direct the sterilised fluid to the waste 147 during the second phase filling the patient, when valve 206 is closed, as well under the third phase emptying the drain bag.

In Fig. 8, the same components as in Fig. 6 have received the same reference numeral starting with 3 instead of 2. The

inlet tube 304 is provided with a branch line 316 ending in a storage bag 317. When valve 306 is closed during the first, second and third phase, the steriliser 100 delivers PD solution into storage bag 317 via tube 316. The heater bag 302 may then be filled much faster from the storage bag 317 compared to the embodiment of Fig. 6. Thus, the heater bag fill phase may be reduced to 2 minutes or less. The efficiency of the complete device becomes dependent only on the cycler and its capacity to drain and fill the patient. The surplus time is merely 4 minutes, 2 minutes for emptying of the drain bag and 2 minutes for filling the heater bag. The procedure has to be controlled if the steriliser is operated in the sequential mode as described in connection with Fig. 5, since the filling of heater bag has to start only when the concentrations are correct in storage bag 317, i.e. after the completion of a complete fill cycle from the steriliser.

The storage bag may also be used as an entry point for addition of medicaments or other additions, like insulin, antibiotic drugs, potassium chloride etc.

It is recognised that the PD solution produced according to the steriliser in Fig. 5 will produce sterile bicarbonate fluid and enter it in the storage bag 317, and then produce sterile glucose solution and subsequently enter that in the storage bag 317. Since the glucose fluid has a low pH, some of the bicarbonate will react and form carbon dioxide, which may be released as a gas. Thus, storage bag 317 is provided with a valve and tube arrangement 318 to indicate when there is surplus gas in the storage bag 317 and expel it to the atmosphere. Another means for doing the same would be to include a sterile filter or hydrophobic filter at the top of storage bag 317. The gas may be expelled in a time interval when outlet valves 138 and 140 are opened (the position shown in Fig. 5) and pressure chamber 301 has an overpressure and valve 306 is open to exert an overpressure into storage bag 317 and expel gas therein.

In the above example indicated in connection with Fig. 5, the bicarbonate concentrate was sterilised at a concentration of about 140 mmol/litre(1000x20/140). However, there is a risk that carbon dioxide is formed during heat sterilisation at such

a concentration, and thus, the concentrate pump may be operated at a lower speed during sterilisation of bicarbonate fluid.

In Fig. 5, the concentrate fluid is preheated to quite a high temperature. This is performed in an efficient heat exchanger 121 in which the heating fluid is the final sterilised fluid in the secondary circuit of the heat exchanger. Thus, the heat exchanger cannot have any point with higher temperature than the sterilising temperature, and decomposition of the heat sensitive component is minimised. The further heating to the final sterilisation temperature, i.e. from about 131°C to about 141°C takes place by the method of mixing with a fluid having a slightly higher temperature. Thus, the heat sensitive fluid component is never exposed to harsh conditions, such as hot points having excessive high temperatures, as may appear in an electric heater 123. Thus, favourable conditions for less formation of degradation products are obtained. The temperature difference between the primary and secondary circuits of the heat exchanger is about 10°C, which is possible to obtain without excessive long residence times in the heat exchanger.

In Fig. 5, there is a circuit not previously described for sterilising the equipment before use. In water line 115, a parallel circuit to valve 120 and heat exchanger 121 is arranged comprising valve 150 and the primary circuit of heat exchanger 143. When heat disinfection of the complete steriliser 100 is to be performed before a treatment, valve 120 is closed, valve 150 is opened and heater 123 is operated. The water passes from pump 117 via valve 150 to heat exchanger 143 and further to heater 123 to be heated to a temperature of, for example, 141°C. The hot water passes heat exchanger 121 but is not cooled appreciably since the primary circuit of exchanger 121 is disconnected and has no flow. The hot water after heat exchanger 121 passes through line 133 and via valves 138 and 141 to heat exchanger 143 to give off its heat to the water passing at the primary side thereof. Finally, the water is discharged to the waste via restrictor device 145, which lowers the pressure from about 2 - 6 Bar to atmospheric pressure.

Thus, the on-line autoclave is self-sterilised and is ready for producing PD fluids. The self-sterilising step may

be performed in about 30 minutes and is initiated under program control to happen shortly before the start of a PD treatment, which is scheduled in advance by a patient. When the self-sterilisation process is ready, the machine awaits the arrival of the patient, which connects a disposable set, such as set 200 or 300 to the outlet connector 139. Then, the device produces a quantity of sterile treatment fluid into heater bag. However, before the patient is connected to connector 208, the tubes should be filled with fluid to displace the air therein. This is performed by attaching the connector 208 to a hook or attachment device on the cycler at approximately the same level as the heater bag. Then, valve 209 is opened to allow fluid to flow through tube 207 to patient connector 208. Then, the connector 208 is ready for connection to the patient.

It is appreciated that the priming procedure described above takes about 20 minutes, since the heater bag must be filled with 2 litres of solution. If this time is too long for the patient to wait, it is possible to perform a partial fill of the heater bag with for example 5 dl solution produced in 4 minutes, and use this volume of fluid to prime the tubes and displace the air. Then, the patient may connect himself to the connector 208 already after 4 minutes of priming and then go to bed, while the machine produces the first fill volume. It is noted that there is normally 2 - 4 dl of solution left in the heater bag, in order to prevent complete emptying of the heater bag, because there is often some air or gas in the top of the heater bag, which should not be delivered to the patient. The first priming solution may be different from the treatment solution, for example comprising physiological sodium chloride.

Several embodiments of the invention have been described above with reference to the enclosed drawings. It will be realised that the different features may be combined in different manners than indicated and such other combinations are within the scope of the invention. The invention is only limited by the appended patent claims.

PATENT CLAIMS

1. A method of sterilising a heat sensitive fluid, **characterised** by:

providing the fluid as a first component, which is heat sensitive, and a second component;

heating the second component to a first temperature higher than a predetermined sterilising temperature;

mixing the first component with the second component to thereby heat the first component and cool the second component, whereby the mixed components obtain a mixing temperature, which is at least equal to said sterilising temperature;

maintaining said mixed components at substantially said sterilising temperature during a sterilisation time so that a predetermined sterilisation dose is obtained; and

delivering said mixed component to a recipient.

2. A method as claimed in claim 1, **characterised** by

controlling the step of heating to the first temperature to obtain a mixing temperature, which is at least equal to said sterilising temperature.

3. A method as claimed in claim 1 or 2, **characterised** by

cooling said mixed components before delivery to said recipient.

4. A method as claimed in claim 1, 2 or 3, **characterised** in that said first component comprises glucose or a glucose polymer.

5. A method as claimed in any one of the previous claims, **characterised** in that said second component comprises water.

6. A method as claimed in claim 5, **characterised** in that said second less heat sensitive component comprises water and includes electrolytes, selected from the group of substances comprising: sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium bicarbonate and sodium lactate.

7. A method as claimed in any one of the previous claims, **characterised** in that said first component is preheated.

8. A method as claimed in any one of the previous claims, **characterised** in that said first and second components are maintained at a high pressure sufficient to prevent boiling of the fluids.

9. A method as claimed in any one of the previous claims, **characterised** in that said first and second components are provided as flows of fluid.

10. A method as claimed in claim 9, **characterised** in that the flow rate of the second component is larger than the flow rate of the first component.

11. A method as claimed in claim 9 or 10, **characterised** by determining the flow rate with a weighing device or a flow meter and increasing the pressure by a pump.

12. A method as claimed in any one of claims 9 - 11, **characterised** by sequentially sterilising several fluid components of a complex fluid.

13. A method as claimed in claim 12, **characterised** by

providing sources of concentrated fluid components and pure water;

pumping a first concentrated fluid from said sources of concentrated fluids, to increase the pressure thereof;

pumping pure water to increase the pressure thereof and heating said pure water to said first temperature;

mixing said first concentrate and heated pure water and maintaining the mixed fluids at a sterilising temperature for a sterilising time to effect sterilisation;

delivering said sterilised and diluted concentrate fluid to a recipient;

repeating the above method steps for each of the concentrated fluid components, to provide the final complex fluid in the recipient.

14. A method as claimed in claim 13, **characterised** in that said concentrated fluid is preheated before being mixed with the heated water.

15. A method as claimed in claim 14, **characterised** in that said preheating is performed in a heat exchanger by heat recovery from the sterilised fluid, which is cooled thereby.

16. A method as claimed in claim 15, **characterised** in that said second fluid is first preheated by heat recovery in a heat exchanger from the sterilised fluid, which is thereby cooled, and is further heated to said first temperature by a separate heating device, such as an electric heater.

17. A method as claimed in claim 16, **characterised** in that said further heating by a separate heating device is controlled by a temperature sensor positioned downstream of the maintaining step, to ensure that sterilising temperature is obtained.

18. A method as claimed in any one of the previous claims, **characterised** by dissolving at least one powdered substance in water to form at least one of the first and second components.

19. A method as claimed in any one of the previous claims, **characterised** by providing the fluid as third component, which is heat sensitive, in addition to said first and second components.

20. A method as claimed in claim 19, **characterised** in that the third component comprises water and at least one amino acid.

21. An apparatus for sterilising a heat sensitive fluid, **characterised** by:

a first vessel enclosing a first component, which is heat sensitive, and a second vessel for enclosing a second component of said heat sensitive fluid;

a first heating device (6) for heating the second component to a first temperature higher than a sterilising temperature;

a mixing device (8) for mixing the first component with the second component to thereby heat the first component and cool the second component, whereby the mixed components obtain a mixing temperature, which is at least equal to said sterilising temperature;

a residence device (9, 10) for maintaining said mixed components at said sterilising temperature during a sterilisation time so that a sterilisation effect is obtained; and

a delivery device (20) for delivering said mixed component to a recipient.

22. An apparatus as claimed in claim 21, **characterised** by

a control device (16, 19) for controlling the heating device to obtain a mixing temperature, which is at least equal to said sterilising temperature.

23. An apparatus as claimed in claim 21 or 22, **characterised** by

a cooling device (13) for cooling said mixed components before delivery to the recipient.

24. An apparatus as claimed in claim 21, 22 or 23, **characterised** in that said first heat sensitive component comprises glucose or a glucose polymer.

25. An apparatus as claimed in any one of claims 21 - 24, **characterised** in that said second less heat sensitive component comprises water.

26. An apparatus as claimed in claim 25, **characterised** in that said second less heat sensitive component comprises water and includes electrolytes, selected from the group or substances comprising: sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium bicarbonate and sodium lactate.

27. An apparatus as claimed in any one of claims 21 - 26, **characterised** by a preheating device (22) for preheating said first component.

28. An apparatus as claimed in any one of claims 21 - 27, **characterised** by a pressurising device (5, 7, 20) for maintaining said first and second components at a high pressure sufficient to prevent boiling of the fluids.

29. An apparatus as claimed in any one of claims 21 - 28, **characterised** in that said first and second components are flows of fluid.

30. An apparatus as claimed in claim 29, **characterised** in that the flow rate of the second component is larger than the flow rate of the first fluid flow component.

31. An apparatus as claimed in claim 29 or 30, **characterised** by a weighing device or a flow meter for determining the flow rate and pump devices for increasing the pressure.

32. An apparatus as claimed in any one of claims 29 - 31, **characterised** by a device for sequentially sterilising several fluid components of a complex fluid.

33. An apparatus as claimed in claim 32, **characterised** by an assembly of bags (105, 106, 107) of concentrate fluids for providing sources of concentrated fluid components and pure water from an inlet (101);

a concentrate pump (129) for pumping a first concentrated fluid from said sources of concentrated fluids, to increase the pressure thereof;

a water pump (117) for pumping pure water to increase the pressure thereof and a heating device (121) for heating said pure water to said first temperature;

a mixing device (124) for mixing said first concentrate and heated pure water and a residence device (134) for maintaining the mixed fluids at a sterilising temperature for a sterilising time to effect sterilisation;

delivery means (139) for delivering said sterilised and diluted concentrate fluid to a recipient, such as a bag;

control means (111) for controlling and repeating the above steps for each of the concentrated fluid components, to provide the final complex fluid in the recipient.

34. An apparatus as claimed in claim 33, **characterised** by a preheater (121) for preheating said concentrated fluid before being mixed with the heated water.

35. An apparatus as claimed in claim 34, **characterised** by a heat exchanger (121) for heat recovery from the sterilised fluid, which is cooled thereby.

36. An apparatus as claimed in claim 35, **characterised** by a heat exchanger for preheating said second fluid by heat recovery from the sterilised fluid, which is thereby cooled, and a heater (123) for further heating to said first temperature.

37. An apparatus as claimed in claim 33, **characterised** in that said heater (123) is adapted to be controlled by a temperature sensor (136) positioned downstream of the residence device (134), to ensure that at least sterilising temperature is obtained.

38. An apparatus as claimed in any one of claims 21 - 37, **characterised** in that at least one of said first and second vessel comprises at least one powdered substance for dissolution in water to form at least one of the first and second components.

39. An apparatus as claimed in any one of claims 21 - 38, **characterised** by a third vessel comprising a third component, which is heat sensitive.

40. An apparatus as claimed in claims 39, **characterised** in that the third component comprises water and at least one amino acid.

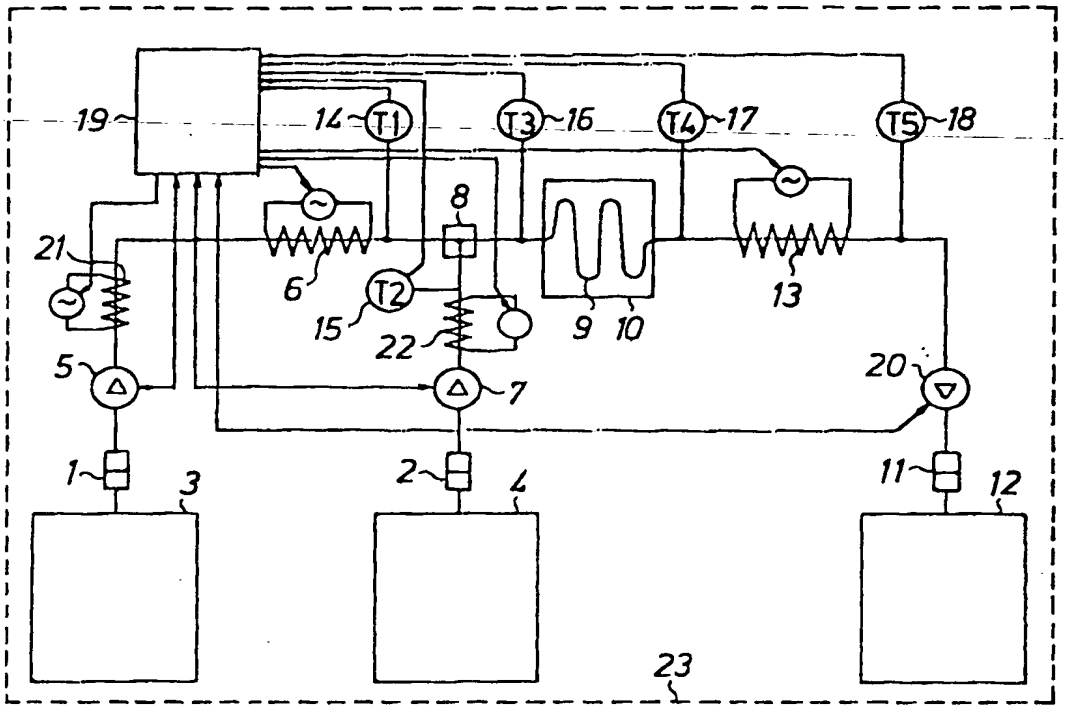
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FIG. 1

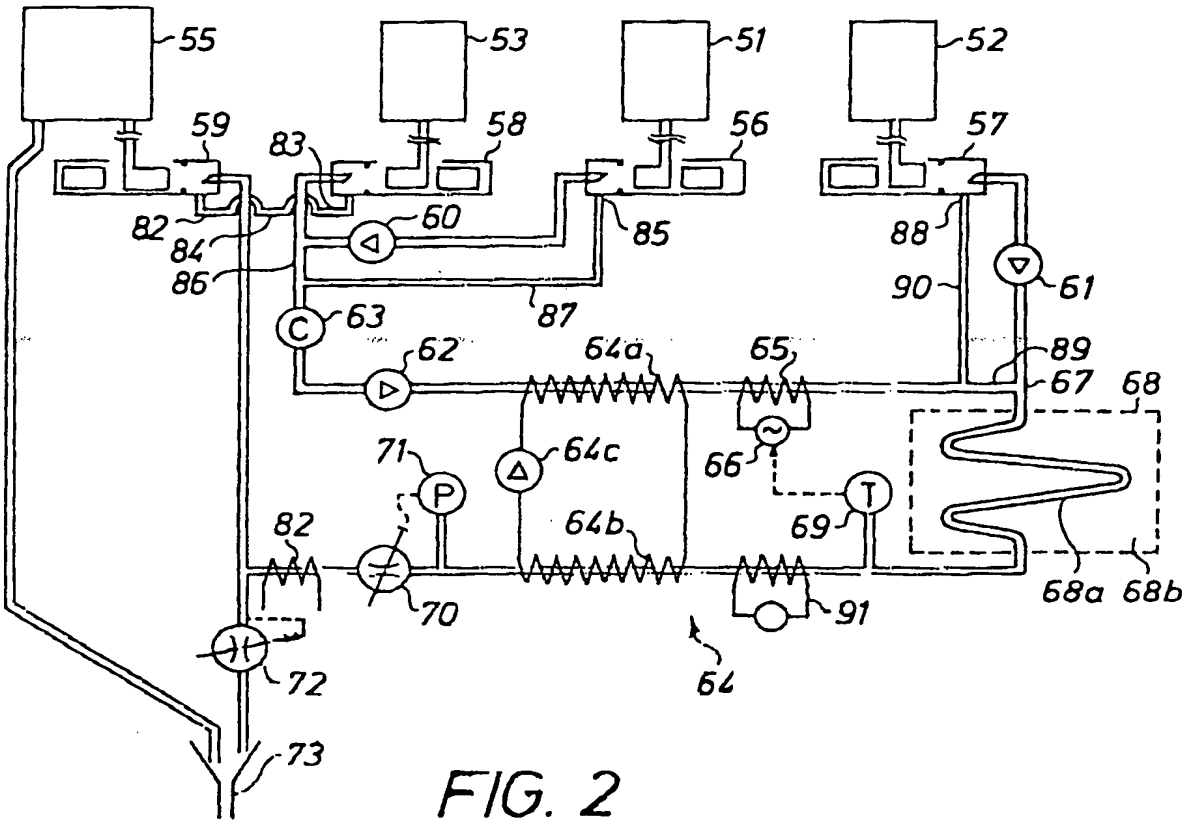
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FIG. 2

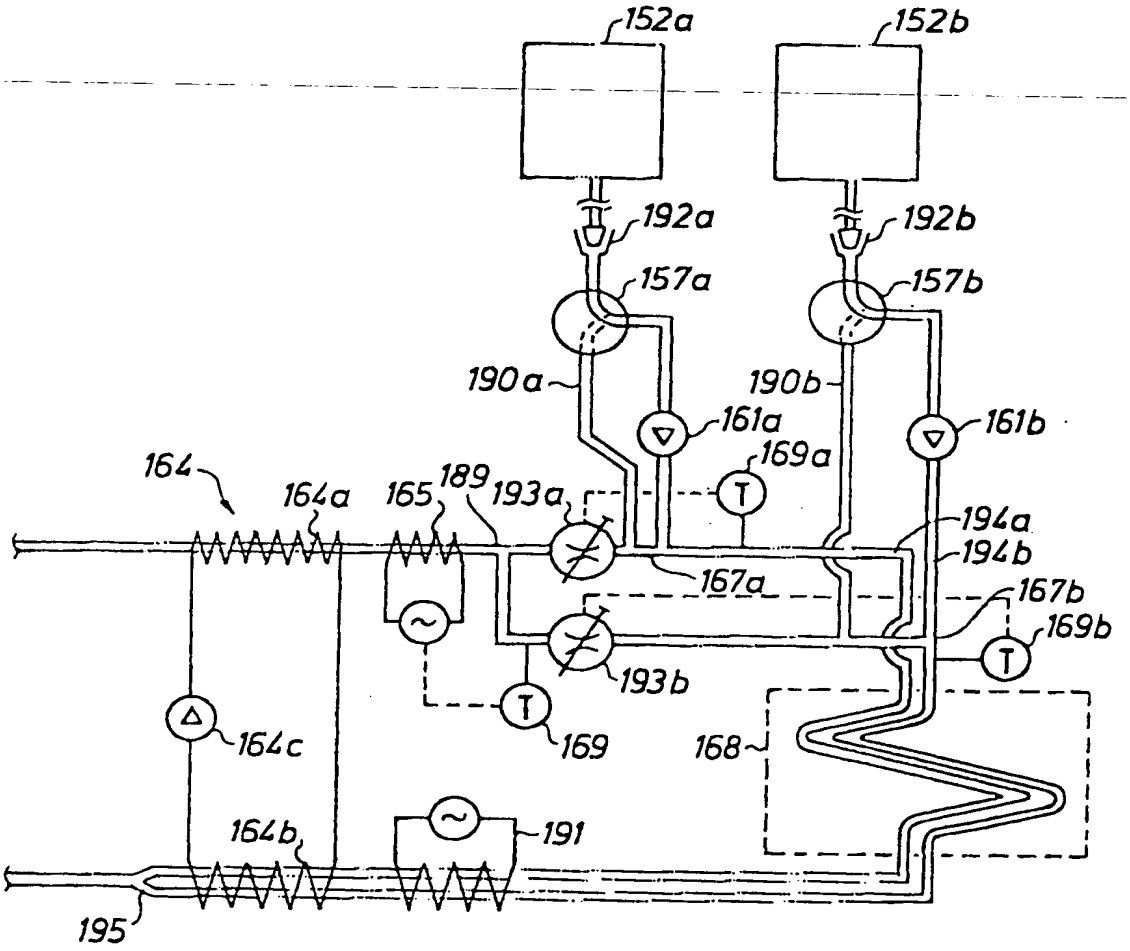
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FIG. 3

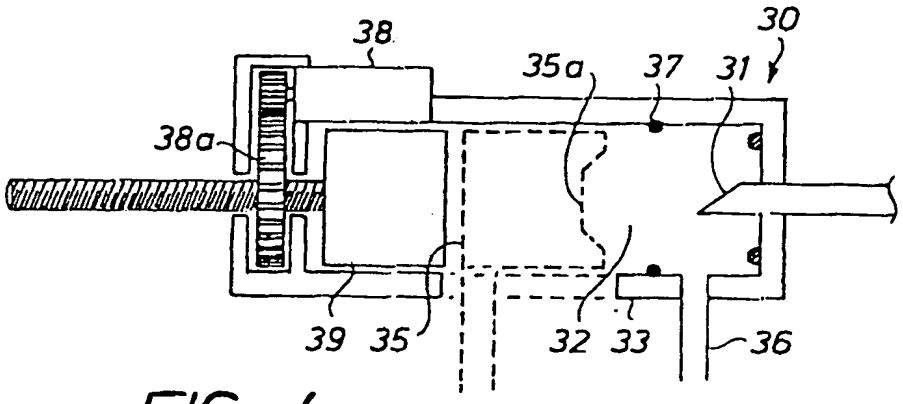
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FIG. 4

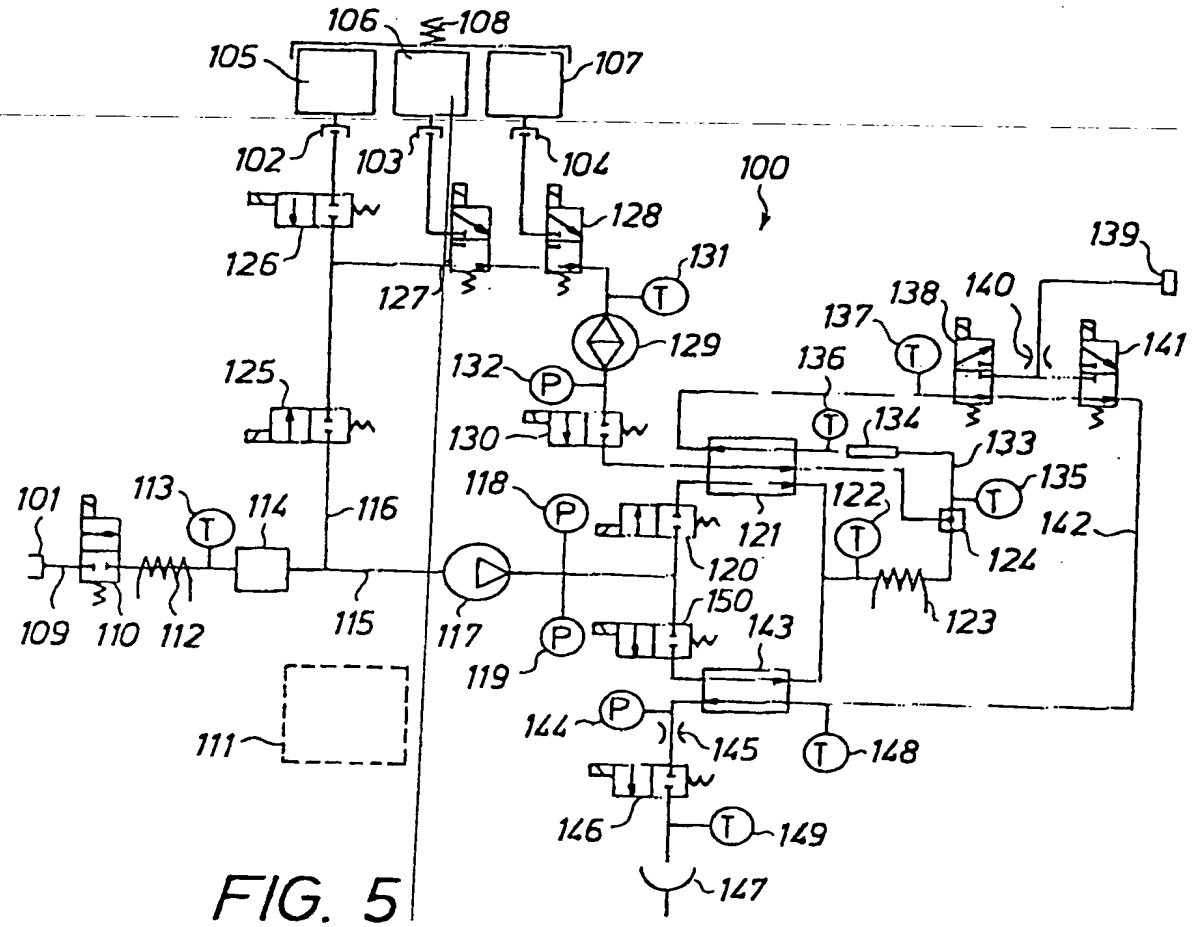
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FIG. 5

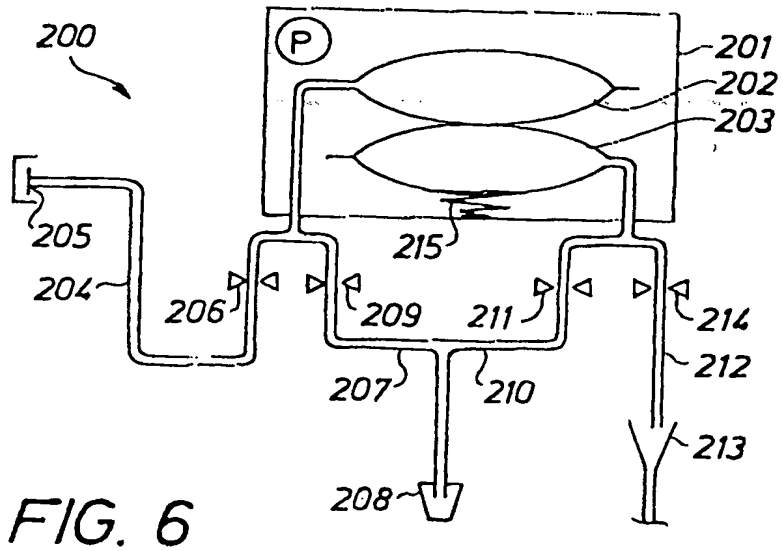
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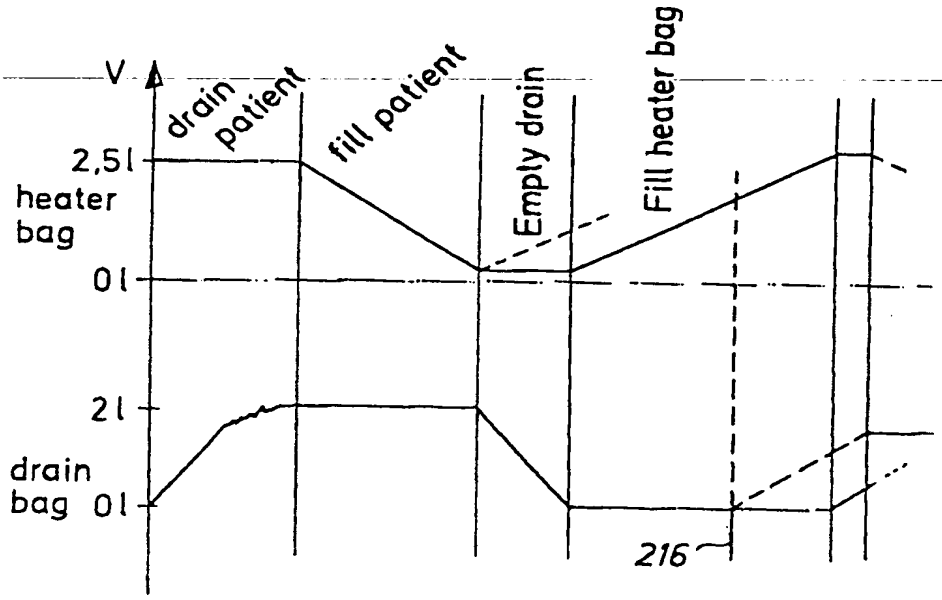
FIG. 6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fill patient
Empty drain
Fill heater bag
2,5l
heater bag
0l
2l
drain bag 0l
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FIG. 7

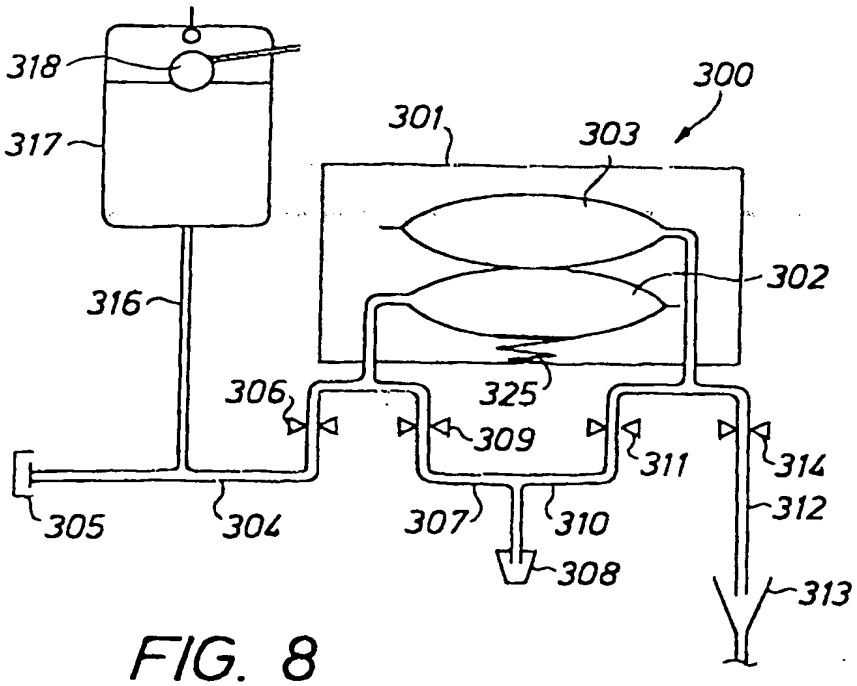
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FIG. 8